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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER				
KUDLA, JOSEPH S				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/522,259

Applicant(s)

SHI ET AL.

Examiner

Joseph S. Kudla

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 January 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16, 18 and 30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16, 18 and 30 is/are rejected.
- 7) ☒ Claim(s) 1 and 15 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-85/06)
Paper No(s)/Mail Date 1/25/05, 11/09/07 and 12/3/07.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
- 5) ☐ Notice of Informal Patent Application.
- 6) ☐ Other: _____.

Election/Restriction

1. Applicant's election without traverse of the two elections of species and a disorder in the reply filed on December 3, 2007 and January 30, 2008 is acknowledged.
2. Applicant's December 3, 2007 correspondence elects (2R)-5-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid as the compound of instant claim 1, atorvastatin as the HMG-CoA reductase inhibitor of instant claim 30 and hypercholesterolemia as the lipid disorder. The subject matter under consideration is drawn to claims 1-16, 18 and 30.

Priority

3. This application claims priority to PCT Application PCT/US03/23430, filed July 25, 2003, which claims priority to U.S. Provisional Patent Application No. 60/399,520, filed July 30, 2002. Priority is acknowledged.

Information Disclosure Statement

4. The Information Disclosure Sheet (IDS) correspondences submitted by Applicant on January 25, 2005, November 9, 2007 and December 3, 2007 are acknowledged and has been reviewed and are proper citations to appear on a U.S. Patent.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-16, 18 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method of treating a lipid disorder, specifically hypercholesterolemia, with any compound and the specification does not reasonably provide enablement for the use of the composition with or without a second active agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without undue experimentation to treat a sleep-related breathing disorder with cisapride. This is an Enablement rejection.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement

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means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the claims is broad with respect to the number of disorders that are modulated by PPAR α agonists, as claimed. The disorders, such as dyslipidemia, hypercholesterolemia, low HDL levels, and high LDL levels, are known in the prior art to be controlled by PPAR α agonistic action, but disorders such as hyperlipidemia and hypertriglyceridemia appear to be controlled by

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PPAR δ . The breadth of claim 18 exacerbates the complex nature of the subject matter under consideration.

The nature of the invention and the state of the prior art

The claimed invention relates to compounds that are useful as PPAR α agonists. These compounds have been claimed in the instant invention to have the ability to treat lipid disorders, specifically hypercholesterolemia, in a patient. In addition, Applicant has claimed a pharmaceutical compound that has the mechanism of action of a PPAR α agonist, specifically (2R)-5-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid, and a second active ingredient, specifically the HMG-CoA reductase inhibitor atorvastatin in claim 30.

The state of the art is relatively high with regard to attributing the mechanism of action underlying the purported biological activity for each of the various PPAR sub-types (see Willson et al., "The PPARs: From Orphan Receptors to Drug Discovery," 2000, Journal of Medicinal Chemistry, Volume 43, number 4, Pages 527-550 and cited by Applicant). Within the prior art it is well known that PPAR α agonists improve the lipid profile and alleviate dyslipidemias by reducing elevated LDL levels, reducing elevated triglyceride levels, and increasing HDL levels. PPAR γ agonists improve insulin sensitivity, reducing the need for insulin secretagogues and insulin injections in patients with NIDDM, and PPAR δ appears to help control hyperlipidemia and hyperglycemia in type 2 diabetic patients. In addition, some PPAR agonist compounds appear to have the

dual activity of PPAR α and γ . However, nowhere in the prior art has it been shown that a PPAR can have the dual activity of PPAR α and δ , as is implicitly claimed for the various lipid disorders recited in instant claim 18. The reference makes the practice of the instant claimed invention unpredictable, in light of the absence of an enabling specification.

The level of predictability in the art

The instant claimed invention is highly unpredictable. Applicant has shown an adequate process for making the compound, (2R)-5-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid, but has not adequately shown a use for the compound as is required in the first paragraph of 35 U.S.C. 112. Due to the general unpredictability in the pharmaceutical art reference mentioned *supra*, coupled with the broad manner in which Applicant intends to use the compound, one of ordinary skill in the art would not have expected the recited indications of the compound on its face. Applicant would need to show evidence of the likelihood that claimed compounds exhibit the recited physiological responses through examples or scholarly discussion. A nexus between what is commonly known in the art and that which Applicant asserts is his invention is required. The prior art is silent and the discussion by Applicant to the feasibility of the compound to act as any PPAR sub-type agonist or to treat any lipid disorder would have lead one of ordinary skill in the art to believe the invention is speculation. No studies were conducted with any specified PPAR compound to establish the sub-type

mechanism of action nor has it been shown that the compound could treat any lipid disorder. Therefore, one cannot reasonably predict the ability of the claimed compounds to elicit any pharmacological response because the results are neither exemplified in Applicants' specification nor shown in the prior art.

Applicant is reminded of the decision *Genentech Inc. vs. NovaNordisk* which states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting the claimed therapeutic regimen for the treatment of a lipid disorder. *In re Fisher*, 427 F. 2d, 833, 166 USPQ 18 (CCPA 1970), indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Hence, one of skill in the art is unable to fully predict the ability of the elected compound to treat any lipid disorder.

The amount of direction provided by the inventor and the existence of working examples

The instant specification does not provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to practice the claimed methods commensurate in the scope with the

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instant claims. Applicant provides no guidance using the elected compound to treat any lipid disorder. Applicant has also failed to provide any guidance demonstrating in either the prior art or by exemplification that the elected compound has the purported PPAR agonistic activity. Adequate enablement requires more than a mere statement that a compound treats a given condition.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation (*In re Wright*, 999 F. 2d 1557, 1562; 27 USPQ 2d 1510, 1514 (Fed. Cir. 1993)). The specification lacks sufficient disclosure to support applicant's claims of a method for treating any lipid disorder with the elected compound. There is not seen sufficient working examples or data from references in the prior art providing a nexus between that which applicant asserts is supporting a method of treating a lipid disorder with the elected compound and the amount of disclosure Applicant has actually provided.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Based on the unpredictable nature of the invention, the state of the prior art and the breadth of the claims, one skilled in the art could not use the claimed invention without undue experimentation. The essential element towards the validation of a therapeutic modality capable of performing the mechanism of

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action is the ability to test the compound within specific parameters in advance of administration of a compound and, while maintaining experimental control, link those results with sampling time points. Once it can be documented that the compound of interest elicits a desired pharmacological response within experimental controls, the compound, for the sake of this forum, could generally be assumed to have that pharmacological activity. More specifically, once it can be shown that the elected compound exhibits the mechanism of action of an agonist of PPAR α or the dual activity of PPAR α and δ , as is implicitly claimed in instant claim 18, then it may reasonably be concluded it will demonstrate the intended effect of modulating the disorders which are claimed.

Applicant discloses a study (see PPAR Binding Assays on pages 25 and 26) to determine the PPAR sub-type of the compounds. However, Applicant never discloses any examples with any compounds. Applicant discloses a study (see *In Vivo* Studies on pages 27 through page 29) where a test compound was administered to various mammals to monitor such parameters as plasma glucose, triglyceride levels and lipid modulation in response to the administration that test compound. However, Applicant never discloses any specific compound.

As stated in MPEP §2164.04[R-1], "Doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation." In the instant case, the information that is missing is a clear correlation between the claimed compound and its efficacy in treating the claimed disorder, either through specific evidence in the form of data

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demonstrating such a fact or at least a sound mechanistic correlation between the claimed compound, its ability to function in such a manner and the amenability of the claimed disorder to treatment using an agent capable of functioning in this manner. Though one of skill in the art might very well know how to treat a patient with the claimed compound once a diagnosis had been made of the claimed disorder (i.e., high cholesterol), it remains that the instant specification conspicuously fails to provide any guidance or direction in support of the reasonable expectation of success in actually effecting the treatment of the claimed disorder using the claimed compound, in the absence of any evidence supporting the allegation that the claimed compound is, in fact, effective to achieve such a therapeutic objective, either by reduction to practice or at least by elucidating the mechanism by which the claimed compound works and correlating such activity to therapeutic improvement of the claimed disorder. In the absence of this information, the specification fails to provide adequate guidance and/or direction to one of skill in the art at the time of the invention that would have enabled such a person to practice the instantly claimed invention without having to resort to undue experimentation to determine how, in fact, one would achieve the instantly claimed therapeutic objective.

Based on the unpredictable nature of the invention and the state of the prior art, one skilled in the art could not use the claimed invention without undue experimentation.

No claim is allowed.

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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph S. Kudla whose telephone number is (571) 270-3288. The examiner can normally be reached on 9am - 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Joseph S. Kudla/
Examiner, Art Unit 1611
March 22, 2008

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614